REMARKS

Claims 2-18 and 29 are pending in the case. The Applicants have amended Claim 17 to particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. Support for the present amendments is found throughout the specification and claims, as originally filed. No new matter has been added and no additional claims fees are believed to be due. The Applicants believe that the instant amendments have placed the present application in condition for allowance. Accordingly, favorable and timely action is respectfully requested.

Rejection under 35 USC § 112, Second Paragraph

The Examiner has rejected Claims 2, 3 and 29 under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserts that the Applicants have not defined the compounds encompassed by the term "2-decarboxy-2-phosphinico derivatives and salts, hydrolysable amides, esters and imides thereof." For purposes of examination, the Examiner has interpreted the term to include 2-decarboxy-2-phosphinico derivative prostaglandins obtained by coupling of phosphonic acid to the 2-decarboxy prostaglandins (*i.e.* Formulas I to III on page 16 of the present specification).

Indeed, the Applicants submit that the term "2-decarboxy-2-phosphinico derivatives" is intended to refer to all 2-decarboxy-2-phosphinico derivatives of prostaglandins obtained by the process step of coupling a phosphinic acid to a 2-decarboxy prostaglandin. Further, the aforementioned term is specific to prostaglandins and is intended to encompass commonly produced pro-drugs. Moreover, the salts, hydrolysable amides, esters and imides disclosed in relation to the aforementioned term may only be synthesized subsequent to the above-discussed coupling step. Thus, the salts, hydrolysable amides, esters and imides disclosed herein, obtained only after synthesis of a novel and non-obvious composition of matter, possess novelty in their own right. Accordingly, reconsideration and withdrawal of the rejection to Claims 2, 3 and 29 under 35 USC § 112 are respectfully requested.

Rejection under 35 USC § 112, Second Paragraph

The Examiner has rejected Claim 17 under 35 USC § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserts that the phrase "component C) is present in an amount of 1 to 20% of component C)" is vague and indefinite. Further, the Examiner asserts that the phrase "such that the amounts of components A), B) and C), combined equal 100%" is indefinite. The Applicants wish to direct the Examiner's attention to the "Amendments" section of the instant paper, in which the Applicants have amend d Claim 17 to clarify that component C) is present in an amount of from 1% to 20% by weight of the total composition and that the total weight of components A), B) and C) is equal to 100% of the composition. Reconsideration and

withdrawal of the rejection to Claim 17 under 35 USC § 112 are therefor respectfully requested.

Rejection under 35 USC § 102(b) over Biddlecom

The Examiner has rejected Claims 2-10, 12, 14 and 15 under 35 USC § 102(b) as allegedly being anticipated by US Patent Number 4,171, 331 to Biddlecom et al (hereinafter "Biddlecom"). Specifically, the Examiner asserts that Biddlecom discloses 1 and 2-substituted analogues of E, A, and F prostaglandins, which purportedly includes the present phosphonic derivatives of Formula III. The Examiner's rejection is respectfully traversed.

The Applicants wish to note and underscore to the Examiner that the Applicants lay claim to a phosphinic acid, rather than the phosphonic acid compounds disclosed by Biddlecom. As a subsequent section of the instant paper will reveal, the differences between these two compounds are quite significant, particularly when considered in light of the fact that the latter, phosphonic acid compounds have been demonstrated to be devoid of meaningful activity, and thus, ineffective in the context of the present invention. Moreover, the Applicants, via their vast research and development of the present invention, have learned that the high acidity of phosphonic acid compounds discourages their penetration into the lipid-rich membrane of target cells. The Applicants have further and surprisingly discovered that some degree of protonation is required for the administration of the subject prostaglandin into target cells.

The Applicants respectfully direct the distinguished Examiner's attention to the pending claims, and specifically Claim 3. It is clear from the Applicants' definition of the various R group substituents of the general structures claimed therein that it is impossible for the Formula III compound to take the form of a phosphonic acid. To be inclusive of phosphonic derivatives, the R_1 and R_3 substituents of the Formula III compound would both have to be oxygen-containing moieties. On the contrary, the Applicants have explicitly limited the Markush group of R_1 to include only hydrogen, lower monovalent hydrocarbon groups and lower heterogeneous groups. Thus, it is clear then that Formula III of the present invention cannot take the form of phosphonic acid, and therefore, cannot be anticipated by Biddlecom's disclosure of a phosphonic acid compound. Accordingly, reconsideration and withdrawal of the rejection to Claims 2-10, 12, 14 and 15 under 35 USC § 102(b) are respectfully requested.

Rejection under 35 USC § 103(a) over Kende in view of Johnstone

The Examiner has rejected Claims 2-10, 12, 14-18 and 29 under 35 USC § 103(a) as allegedly obvious over Tetrahedron Letters by Kende et al (hereinafter "Kende") in view of US Patent Number 6,262,105 to Johnstone (hereinafter "Johnstone"). Specifically, the Examiner asserts that it would have been obvious for one of ordinary skill in the art to incorporate the requisite carriers and other dermatologically acceptable components of Johnstone into the phophonic derivative prostaglandin-containing hair stimulating compositions of Kende. The Examiner's rejection is respectfully traversed.

Initially, th Applicants wish to note and underscore to the Examiner that the Kende r ference documents the research of the first-named inv ntor of the present application, Mitchell deLong. Indeed, Mr. deLong is listed as an author of the Kende reference. By way of background, Mr. deLong, in his research and development of suitable prostaglandin d rivatives, directed the synthesis of phosphonic acid derivativ s of prostaglandins $F_{1\alpha}$ and $F_{2\alpha}$ via implementation of a confidential disclosur agreem nt with Mssrs. Andr w Kende and Jared Milbank of the University of Rochester. To reiterate, the sole purpose of the agreement was to direct the synthesis of phosphonic acid by the University of Rochester. Upon their completion of the synthesis of phosphonic acid, the University of Rochester remitted the synthesized compound to The Procter and Gamble Company for examination, again at Mr. deLong's direction, to determine the activity of the subject phosphonic acid. Such testing revealed that the subject phosphonic acid is devoid of meaningful activity, and thus, ineffective as a suitable prostaglandin derivative for purposes of the present invention.

As revealed by a previous section of this instant paper, further investigation at the direction of Mr. deLong of the compound synthesized by the University of Rochester (and embodied in the Kende paper) established that the synthesized phosphonic acid compound was too acidic to function effectively as a prostaglandin derivative for use in the present invention. Based on his further investigation of the synthesized phosphonic acid compound, Mr. deLong surprisingly discovered that a moderated level of acidity would be required to nable a subject prostaglandin derivative to penetrate the lipid-rich membrane of target cells. Mr. deLong surprisingly discovered that the phosphinic acid compounds of the present invention possess the appropriate degree of protonation and moderated acidity with which to penetrate the membrane of the target cells. Thus, the Applicants respectfully submit that Kende's disclosure of the synthesis of phosphonic acid, initiated and directed by the first-named inventor of the present application, cannot be used to render obvious the phosphinic acids disclosed and claimed by the same inventor herein. In light of the fact that Kende discloses a compound of an entirely different character than that of the claimed pohsophinic acid compound, the Applicants do not believe it necessary to address its attempted combination with the Johnstone reference. Rather, reconsideration and withdrawal of the rejection to Claims 2-10, 12, 14-18 and 29 under 35 USC § 103(a) are respectfully requested.

Rejection under 35 USC § 103(a) over Biddlecom

The Examiner has rejected Claim 11 under 35 USC § 103(a) as allegedly obvious over Biddlecom. Specifically, the Examiner asserts that Biddlecom teaches prostaglandin analogues, which purportedly include the claimed phophonic derivatives of Formula III for their vasodilator, antihypertensive or antithrombotic activities. The Examiner's rejection is respectfully traversed.

The Applicants again wish to und rscore to the distinguished Examiner that Biddlecom discloses and relates entirely to a substantially inactiv phosphonic acid compound, rather than the active, phosphinic acid prostaglandin derivatives claimed herein. The Examiner's att ntion is again directed to Claim 3 of th instant application, and

specifically Formula III, to which the Examiner makes reference. It is clear from a cursory review of said formula that it is impossible for the claimed, general structure to be inclusive of phosphonic acid, as inclusion of phosphonic acid would require that the substituents R_1 and R_3 both be oxygen-containing moieties. However, the Applicants have defined th substituent R_1 of Formula III to include only hydrogen, lower monovalent hydrocarbon groups and lower het rogeneous groups. Thus, Formula III of th present invention cannot take the form of phosphonic acid, and therefore, can neither be anticipated nor rendered obvious by Biddlecom's disclosure of a phosphonic derivative.

Further, the Applicants wish to underscore to the Examiner that, as the preceding section revealed, the Applicants have determined that the phosphonic acid compounds disclosed by Biddlecom are devoid of meaningful activity, and thus, are not suitable for use in the context of the present invention. The Applicants have discovered that the phosphonic acid compound is too acidic to penetrate the lipid-rich membrane of target cells. The Applicants have surprisingly discovered that the present phosphinic acid compounds, possess the moderated level of acidity and partial protonation required for their penetration of the membrane of target cells. Thus, the Applicants submit and strongly urge that it would not have been obvious to a person of ordinary skill in the art, at the time the invention was made, to employ an active, phosphinic acid compound as a prostaglandin derivative for, among other things, the treatment of hair loss, from reviewing Biddlecom's disclosure of a substantially inactive, phosphonic acid compound. Reconsideration and withdrawal of the rejection to Claim 11 under 35 USC § 103(a) are therefore respectfully requested.

CONCLUSION

Attached h reto on a separate sheet is a "Version With Markings To Indicate Chang s Made." Applicants have mad an earnest effort to place the present claims in condition for allowance. WHEREFORE, entry of the amendments provided herewith, reconsideration of the claims as am nded in light of the Remarks provid d, withdrawal of the claims rej ctions, and allowance of Claims 1, 2-12, 14-18 and 29-30, as amended, are respectfully requested. In the event that issues remain prior to allowance of the noted claims, then the Examiner is invited to call Applicants' undersigned attorney to discuss any remaining issues.

Respectfully submitted,

MITCHELL ANTHONY DELONG, et al

By _____

Frank Taffy, *Esq.*
Attorney for Applicants
Registration No. 52,270
(513) 634-9315

Customer No. 27752

25 September 2002
Cincinnati, Ohio
7997-OA.doc

VERSION WITH MARKINGS TO INDICATE CHANGES MADE

17. (Once Amended) The composition of claim 16, wherein component A) is present in the composition in an amount of: $IC_{50} \times 10^{-2} \geq$ % of component A) $\geq IC_{50} \times 10^{-3}$, where IC_{50} is expressed in nanomolar units; component C) is present in an amount of 1 to 20% ~~component C)~~by weight of the total composition, and a sufficient amount of component B) is present such that the total weight of ~~amounts of~~ components A), B), and C), ~~combined~~ is equal 100% of the composition.